Detection of residual dipolar couplings by 2D MRS techniques in skeletal muscle

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Introduction: There is great interest in detecting the IMCL and EMCL lipid pools in skeletal muscle due to their correlation with disorders of glucose homeostasis, including insulin resistance and diabetes. In addition, localized 2-D correlation spectroscopy has recently been demonstrated to provide an estimate of the degree of unsaturation within the IMCL and EMCL lipid pools by evaluation of cross peaks generated by *J* couplings between the olefinic, allylic, and diallylic methylene protons (1). In this study, we demonstrate the feasibility of detecting the residual dipolar coupling between the creatine CH_3 and CH_2 along with *J* interactions between the various resonances of IMCL and EMCL lipid pools using two separate pulse sequences, L COSY and 2D *J* PRESS (2, 3).

Methods: An MRI compatible boot made of polyethylene was designed to permit continuous variation in the position of the ankle joint. The boot can be locked at any ankle position during plantar- and dorsiflexion. The position of the ankle at standing position was measured in a subject as the angle created by the line through the medial malleolus and the medial distal head of the first metatarsal bone relative to a horizontal plane. The plantar- and dorsiflexion movements were performed with reference to this neutral angle. Localized L COSY spectra were acquired with TR=2s, TE_{min}= 30ms, 64 t_1 increments with 0.8ms increment increments, 8 averages/t_1 increment with a total acquisition time of 17 minutes from the soleus muscle at neutral, neutral + 45° (plantar flexion), and neutral –20° (dorsiflexion). 2D *J* PRESS experiments were performed at the same angles with similar parameters, using a t_1 incremental period of 5ms. All experiments were performed on a 3 Tesla whole body MRI scanner (GE Signa HD) using an extremity transmit / receive coil.

Results: Figures 1A, 1B and 1C show the L COSY and 2D *J* PRESS spectra acquired from the soleus muscle compartment from a $3cm^3$ voxel during dorsiflexion (neutral - 20°) and plantar flexion (neutral + 45°) angles. The spectra display diagonal and cross peaks generated from saturated and unsaturated groups of IMCL, EMCL lipid pools and other metabolites. We also detected a cross peak centered at [3.03, 3.9 ppm] and [3.9, 3.03 ppm] in the L COSY spectrum (Fig. 1A) which was evident during the dorsiflexion and was absent during plantar flexion at neutral + 45°. All assignments were made as described in earlier work (1). The cross peaks labeled as C1-C6 are due to *J* couplings and the cross peak labeled as D1 is due to the residual dipolar coupling (indicated by arrows in the figures). The cross peak appeared at reduced intensity in the neutral position. The 2D *J* PRESS spectra (Figs. 1B, 1C) also show the various *J* couplings and the residual dipolar coupling (D1) at 3.9 ppm (indicated by arrows). The residual dipolar splitting is reduced at neutral position and the two components of the split line merged during plantar flexion at neutral + 45°. Figure 1C shows the collapse of the dipolar splitting during plantar flexion, again confirming the identity of this peak as representing residual dipolar interaction.

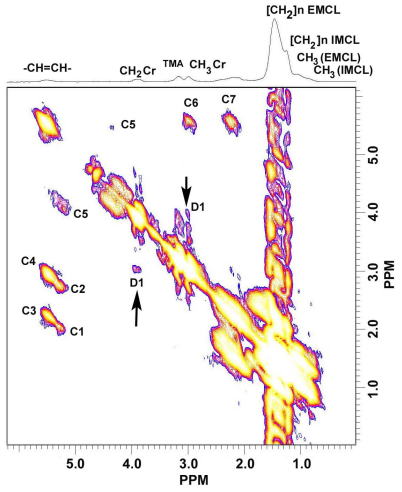

Fig. 1A. L COSY Spectrum from soleus muscle during dorsiflexion

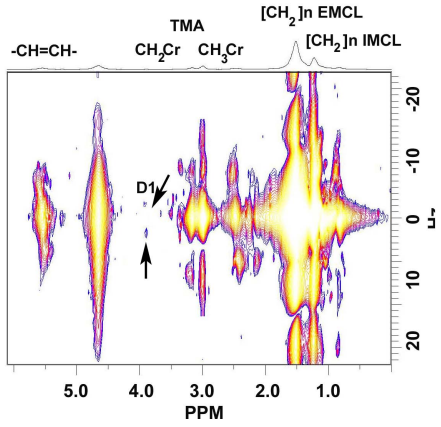

Fig. 1B. 2D J PRESS spectrum from soleus muscle during dorsiflexion

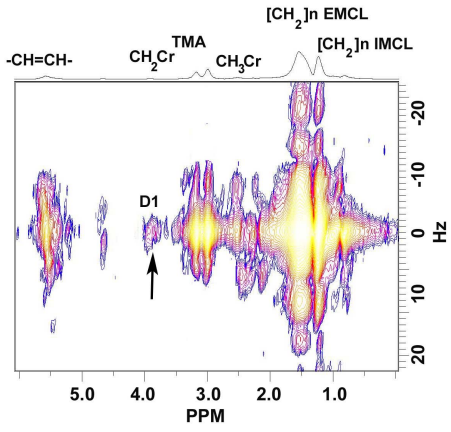

Fig. 1C. 2D J PRESS spectrum from soleus muscle during plantar flexion

Discussion: The cross peaks in a L COSY spectrum can be generated by either *J* coupling as generally observed in isotropic liquids, direct dipole-dipole interaction. The size of the *J* coupling is based on internuclear interactions through fixed bonds, and hence is invariant with respect to molecular orientation. The dipolar coupling, on the other hand, is observable only in oriented media and is diminished when the angle between the internuclear vector and the external magnetic field is close to the magic angle of 54°. Earlier ultrasound experiments have demonstrated that the soleus muscle demonstrates a pennation angle ~ 32°-35° during dorsiflexion in the range of neutral -15° to -30° (4). This pennation angle varies between 40° - 55° during plantar flexion from neutral to neutral + 45°. The cross peak at [3.03, 3.9 ppm] and [3.9, 3.03 ppm] (indicated by arrows) disappeared during the plantar flexion at 45° (near the magic angle) confirming that this cross peak is due to residual dipolar coupling. This cross peak appeared with moderate intensity in the neutral position indicating partial averaging of this dipolar coupling. Similar results were obtained independently with the 2D *J* PRESS experiment, again confirming the presence of residual dipolar coupling.

Conclusion: We conclude that the peak labeled as D1 in the L COSY and 2D *J* PRESS spectra is generated due to residual dipolar interaction between the CH_3 and CH_2 groups of total creatine. The magnitude of this peak is clearly dependent on muscle fiber orientation with reference to the main magnetic field. Our results are consistent with an earlier hypothesis that the elongated spaces between actin and myosin chains of muscle hinder the isotropic tumbling of the creatine molecule (5), resulting in residual dipolar coupling.

References:

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